D6 encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

In the Claims:

Please cancel claim 44, without prejudice.

Please amend claim 39 to read as follows:

D7 39. (Once amended) An antibody that specifically binds to the polypeptide shown in Figure 86 (SEQ ID NO: 245).

Remarks/Arguments

The foregoing amendments in the specification and claims are of formal nature, and do not add new matter.

Prior to the present amendment, claims 39-44 were pending in this application and were rejected on various grounds. Claim 44 has been cancelled. The rejection of the remaining claims is respectfully traversed.

Oath/Declaration

The Examiner alleges that the oath or declaration is defective due to non-initialed and/or non-dated alterations and since it does not identify the citizenship of each inventor.

Applicants submit that a supplemental Application Data Sheet for the above identified application was sent on December 19, 2002 to the USPTO. Hence, Applicants submit that this objection is moot and herewith, provide a copy of the Application data sheet for the Examiner's convenience.

Specification

The specification has been objected to for containing embedded hyperlink and/or other form of browser-executable code. The foregoing amendment, which deleted all embedded hyperlinks, is believed to overcome this objection.

The title was objected to as being non-descriptive. The foregoing amendment, which replaces the original title with a new, descriptive title is believed to overcome this objection.

Claim Rejections – 35 USC §101 and § 112

(1) Claims 39-44 were rejected as allegedly not being supported by either a credible, specific and substantial asserted utility, or a well established utility. According to the rejection, the specification "does not teach any significance or functional characteristics of the PRO293 (SEQ ID NO: 245) polypeptide or antibody. The specification also does not disclose any specific method or working examples for the production of the antibody or labeling of the antibody."

Applicants disagree, and respectfully traverse the rejection.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the

"substantial utility" standard, M.P.E.P. 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, **any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,** at least with regard to defining a "substantial" utility." (M.P.E.P. 2107.01, emphasis added.) Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P, 2107 II (B) (1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, the Utility Guidelines restate the Patent Office's long established position that any asserted utility has to be "credible." "Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record . . . that is probative of the applicant's assertions." (M.P.E.P. 2107 II (B) (1) (ii)) Such standard is presumptively satisfied unless the logic underlying the assertion is seriously flawed, or if the facts upon which the assertion is based are inconsistent with the logic underlying the assertion (Revised Interim Utility Guidelines Training Materials, 1999).

Proper Application of the Legal Standard

Applicants submit that the antibodies claimed in the present application have a specific, substantial and credible asserted utility, which is sufficiently described in the specification.

Applicants rely on the PDB12 cell inhibition data (page 207, lines 2-18) in support of patentable utility. These data were first disclosed in PCT/US98/19330 on September 16, 1998, the priority of which is claimed in the present application.

Example 70 describes a cell-based assay, in which PRO 293 has been demonstrated to have the ability inhibit protein production by PDB12 pancreatic ductal cells, using an alamarBlue™-based cell proliferation assay.

Cell culture models are a valuable tool for life science researchers, since they permit the study of a single cell type, and, through determination of cell proliferation and viability, enable researchers to assess the efficacy of potential therapeutic agents in the prevention and treatment of disease processes associated with the particular cell type studied.

AlamarBlue™-based assays in particular have been widely used in the study of cell proliferation and cell viability. The internal environment of the proliferating cell is more reduced than that of a non-proliferating cell, and the ratios of NADPH/NADP, FADH/FAD, FMNH/FMN, and NADH/NAD increase during cell proliferation. AlamarBlue™ can be reduced by such metabolic intermediates, the reduction is accompanied by a measurable shift in color, which, in turn, can be monitored by measuring absorbance spectrophotometrically, or by measuring fluorescence The assay described in Example 70 of the present application uses fluorescence read-out, which allows one to calculate total cellular protein concentration produced by PDB12 pancreatic ductal cells in the presence and absence of a particular test molecule, such as the PRO 293 polypeptide. Accordingly, the results of this assay can be considered as a secondary read-out for cell number, and are suitable for the assessment of the biological effect of a test substance on pancreatic cells. The data presented in Example 70 clearly demonstrate that the PRO 293 polypeptide inhibits protein production by PDB12 pancreatic cells. Accordingly, agonist antibodies specifically binding the PRO293 polypeptide are useful drug candidates in the treatment of pancreatic disorders where such inhibition is desirable, such as pancreatitis, e.g. chronic alcoholic pancreatitis, which is known to be accompanied by ethanol-induced protein secretory alterations, and increased intraductal protein precipitation. Antagonist anti-PRO293 antibodies find utility, for example, in the diagnosis of such diseases.

The Examiner notes that the PDB12 cell inhibition assay does not provide a usable activity of the anti-PRO293 antibody, since the PDB12 cell inhibition "is not credible, specific or substantial." In support of this conclusion, the Examiner notes that "any slight increase in protein

production, which may even result from the normal variations in cell number, would not indicate that PRO293 specifically inhibits protein production in PDB12 pancreatic ductal cells." The Examiner further argues that in the absence of the disclosure of any specific resulting cell numbers or percentages, statistical differences, or the number of repetitions for the assay, one of ordinary skill in the art at the time the invention was made could would not have been able to use the information obtained from this assay in a useful manner.

As set forth in M.P.E.P, 2107 II (B) (1), if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed. The logic underlying the asserted utility in the present case is not inconsistent with general knowledge in the art, and would be considered credible by a person skilled in the art. It is, of course, always possible that an invention fails on its way of development to a commercial product. Thus, despite recent advances in rational drug design, a large percentage of drug candidates fails, and never makes it into a drug product. However, the USPTO is not the FDA, the law does not require that a product (drug or diagnostic) be currently available to the public in order to satisfy the utility requirement.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) Claims 39-44 were rejected under 35 USC 112, first paragraph for alleged lack of enablement. According to the rejection, "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

In response to the previous rejection, Applicants have shown that the claimed antibodies have a specific and substantial asserted utility, the present rejection should be withdrawn.

Claim Rejections - 35 USC § 112

Claims 39-44 were rejected as "indefinite," since, according to the Examiner, the difference between binding and specific binding (recited in claims 39 and 44, respectively) was not clear. Applicants submit that the art-recognized meaning of "specific" binding is that the antibody that specifically binds to a particular antigen does not significantly cross-react with another antigen. However, solely to simplify issues, and facilitate the prosecution of the present application, claim 44 has been canceled, and claim 39 has been amended to recite specific binding. Accordingly, the present rejection is believed to be moot, and should be withdrawn.

Attached hereto is a marked-up version of the amendments made to the specification and claims, entitled "**Version with markings to show changes made.**"

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-1618P2C32). Please direct any calls in connection with this application to the undersigned at the umber provided below.

Respectfully submitted,

Date: February 27, 2003

Ginger R. Dreger
Reg. No. 33,055

HELLER EHRMAN WHITE & McAULIFFE LLP
Customer No. 35489
275 Middlefield Road
Menlo Park, California 94025
Telephone: (650) 324-7000
Facsimile: (650) 324-0638

Version with markings to show changes made

In the Specification:

The original title has been canceled, and replaced with the following new title:

---- Anti-PRO293 antibodies.--

The paragraph, beginning at page 69, line 6, has been amended as follows:

--Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph, beginning at page 71, line 26, has been amended as follows:

--Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et al., Nucleic Acids Res. 25:3389-3402 (1997)). [The NCBI-BLAST2 sequence comparison program may be downloaded from http://www.ncbi.nlm.nih.gov.] NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = 15/5, multi-pass e-value = 0.01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.--

The paragraph beginning at page 147, line 27, has been amended as follows:

The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to

search EST databases. The EST databases included public databases (e.g., Dayhoff, GenBank), and proprietary databases (e.g. LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altschul, and Gish, Methods in Enzymology 266: 460-80 (1996)[; http://blast.wustl/edu/blast/README.html]) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a Blast score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington).

The paragraph, beginning at page 154, line 14 has been amended as follows:

--The EST sequence accession number AF007268, a murine fibroblast growth factor (FGF-15) was used to search various public EST databases (e.g., GenBank, Dayhoff, etc.) The search was performed using the computer program BLAST or BLAST2 [Altschul et al., Methods in Enzymology, 266:460-480 (1996)[; http://blast.wustl/edu/blast/README.html]] as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequences. The search resulted in a hit with GenBank EST AA220994, which has been identified as stratagene NT2 neuronal precursor 937230.--

The paragraph beginning at page 167, line 30, has been amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the

program "phrap" (Phil Green, University of Washington, Seattle, Washington[; http://bozeman.mbt.washington.edu/phrap.docs/phrap.html]).

The paragraph beginning at page 178, line 14, has been amended as follows:

--The extracellular domain (ECD) sequences (including the secretion signal, if any) of from about 950 known secreted proteins from the Swiss-Prot public protein database were used to search expressed sequence tag (EST) databases. The EST databases included public EST databases (e.g., GenBank) and a proprietary EST DNA database (LIFESEQ™, Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST2 (Altshul et al., Methods in Enzymology 266:460-480 (1996)) as a comparison of the ECD protein sequences to a 6 frame translation of the EST sequence. Those comparisons resulting in a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program "phrap" (Phil Green, University of Washington, Seattle, Washington[; http://bozeman.mbt.washington.edu/phrap.docs/phrap.html]).--

In the Claims:

Claim 44 has been canceled.

Claim 33 has been amended as follows:

39. (Once amended) An antibody that specifically binds to the polypeptide shown in Figure 86 (SEQ ID NO: 245).

SV 419951 v1
2/27/03 1:20 PM (39780.1618)